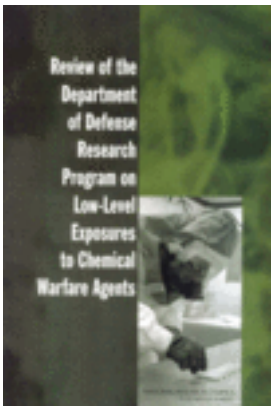
Free Executive Summary



Review of the Department of Defense Research Program on Low-Level Exposures to Chemical Warfare Agents

Subcommittee on Toxicologic Assessment of Low-Level Exposures to Chemical Warfare Agents, Committee on Toxicology, National Research Council

ISBN: 0-309-10021-6, 122 pages, 6x9, paperback (2005)

Research related to chemical warfare agents (CWAs) has historically focused on life threatening battlefield effects caused by high level exposures to the agents, not effects associated with exposures to low concentrations of them. In this report, low level concentrations refers to exposures that may not have any immediate observed health effects, but may produce delayed health effects months or years later. Recently, there has been increased concern about the potential health effects of exposures to CWAs at low concentrations. This report reviews the Department of Defense's (DOD) Research Plan for obtaining toxicologic and other relevant data to assess risk to military personnel. The CWAs of concern include the following nerve and vesicant agents: tabun, sarin, soman, cyclosarin, VX, and sulfur mustard. The report discusses the health effects of exposure to low levels of these agents and provides guidance to DOD on appropriate risk assessment methods for assessing toxicologic risk to military personnel from low-level exposures to CWAs. The report concludes that DOD's Research Plan is well planned and many of the proposed research tasks are likely to provide valuable information to DOD in protecting military personnel.

Summary

Historically, research related to chemical warfare agents (CWAs) has focused on life-threatening battlefield effects caused by high-level exposure to CWAs. In contrast, there are limited data on the adverse health effects associated with exposure to low concentrations of CWAs. Concerns have been raised about the potential health effects of longer-term exposure to CWAs at concentrations lower than those needed to produce effects associated with high concentrations. Such concerns have become a priority of the U.S. Department of Defense (DOD). The threat of low-level CWA exposure includes the following:

- Downwind from or at the periphery of a CWA attack or release.
- Entry or reentry into an area after a CWA release.
- Exposures that occur during decontamination operations or from secondary contamination due to incompletely decontaminated material, supplies, and so forth.
- Exposures after planned but inadequate or improper destruction of CWA munitions.

In response to those concerns, the DOD Low-Level Chemical Working Group was formed to develop research programs within the DOD Chemical and Biological Defense Program to understand the adverse health effects of low-level exposure to CWAs, to defend against low-level exposure, to prevent unnecessary duplication of research efforts, and to focus and direct scientific investigations to address operational issues. The DOD Master Research Plan (Research Plan) devel-

oped for this effort addresses research on operationally relevant performance decrements and delayed adverse health effects that potentially might be associated with low-level exposure to CWAs.

The stated objective of the Research Plan is to characterize the toxicity of CWAs to enable rational military decision making for issues related to doctrine, training, materiel, leadership, personnel, and facilities. The Research Plan includes consideration of the following: (1) decision making in operational risk management for the range of sensitivities needed for detectors, sensors, and alarms; (2) efficiency needed for individual and collective protection systems; (3) effectiveness of decontamination measures and procedures; (4) restoration of normal military operations; (5) return of previously contaminated materiel to "normal" use; (6) operationally relevant performance decrements and adverse long-term health sequelae; (7) as yet unrecognized outcomes of exposure; and (8) medical diagnostics, prophylaxes, pretreatments, and treatments.

The Research Plan describes DOD's planned research on low-level exposure from Fiscal Year 2002[1] (FY 2002) to FY 2007 that has been or is to be conducted within the existing framework of the DOD Chemical and Biological Defense Program. Every study proposed under the Research Plan is designed to answer one mandatory question: How do data from this work contribute materially toward a quantitative refinement of the human health risk assessment for low-level CWA exposure? The Research Plan is based on three major research thrusts:

- Characterize concentration-time relationships for low-level and longer-time CWA vapor exposures.
- Identify alternative, but physiologically significant, toxicologic end points.
- Conduct appropriate integration studies linking experimental data sets with predictive human health-effect risk assessments.

[1] Prior to 2002, bits and pieces of the research on low-level exposure to CWAs were being done by various departments of the DOD. In 2002, the DOD formalized all the research on low-level exposures in the Department of Technology Office (DTO) of the DOD, and a time line was created to complete various kinds of research by DOD by 2007.

BACKGROUND

In section 247 of the 1999 Defense Authorization Act, the U.S. Congress directed the Secretary of Defense to review and modify DOD policies and doctrines that relate to protecting personnel from low-level exposure to CWAs. In response to that congressional mandate, the Secretary of Defense directed DOD's Nuclear, Chemical, and Biological Defense Program to develop a Research Plan to obtain toxicologic and other relevant data to assess risk to military personnel. According to DOD, the Research Plan is intended to accomplish two objectives. The first is to support operational commanders in the field with information for real-time decision making required to accomplish their missions while not unduly jeopardizing the health and performance capability of their forces. The second is to understand and prevent or reduce operationally relevant performance decrements as well as the potential health consequences of low-level exposure that may not manifest immediately but may become evident months or years after the exposure.

For the Research Plan, CWAs of initial concern are nerve and vesicant agents. Nerve agents include tabun (GA), sarin (GB), soman (GD), cyclosarin (GF), and VX. The vesicant agent of concern is sulfur mustard (HD). Exposure duration and frequencies to be considered are those likely to be experienced by deployed military personnel. Concentrations of interest are those at which no observable adverse health effects (immediate or delayed) are expected for healthy military personnel, as determined by accepted toxicologic tests and standard medical practices. Performance decrements significant to personnel carrying out their military duties are of greater concern than delayed health effects and therefore are assigned a higher priority.

CHARGE TO THE COMMITTEE

The committee's tasks were to review research proposed in the Research Plan, to provide recommendations about that research, and to develop recommendations for additional research as appropriate. The committee's tasks also include providing guidance to DOD on appropriate risk assessment methods for assessing toxicologic risk to military personnel from low-level exposure to CWAs.

THE COMMITTEE'S CONCLUSIONS AND RECOMMENDATIONS

The committee's major conclusions and recommendations concerning the Research Plan are presented below.

- The committee concludes that DOD's master research plan on low-level exposure to CWAs, in general, is well planned and many of the proposed research tasks are likely to provide valuable information in protecting the military personnel from low-level exposure to CWAs and avoiding performance decrements. The Research Plan includes some studies that have some potential to identify delayed adverse health effects, but those studies should be assigned lower priority in the context of DOD's primary objectives. Available information to date do not provide a sound basis for anticipation of delayed adverse health effects following low-level (in particular, short-term) exposure to nerve agents. However, the committee recommends that a small portion of DOD research budget be allocated to some research tasks to rule out the possibility of delayed health effects.
- For DOD, an important task is also to identify the highest concentration of CWA to which an unprotected person can be intermittently or continuously exposed without immediate or delayed health effects. Exposures should range from 1 hour to 1 year, the focus being on acute (short-term, high-level) single exposures and those repeated over 2 weeks.
- Although miosis (pupil contraction) has typically been considered the critical effect and most frequently used indicator of toxicity, questions about other adverse effects at low concentrations of exposure remain. DOD should conduct research to identify whether there are more sensitive toxicity end points from exposure to low concentrations of CWAs.
- If miosis is selected as the critical adverse response, studies must determine what level of pupillary constriction in miosis is operationally relevant. This information is needed for operational risk management and risk-risk comparison, which must consider the range of exposure limits and the probability of adverse outcomes for exceedances of those exposure limits for various levels of toxicity severity and operationally relevant exposure durations. Miosis studies in laboratory animals should include instillation of CWAs in eyes, using appropriate dose ranges, for correlation with cholinesterase inhibition in eyes. Because

ambient light levels confound pupillary effects of CWAs, the committee recommends that the effects of CWAs be determined under known lighting conditions. Furthermore, a rapid and accurate sensor of both miosis and ambient light will be needed to provide information necessary for field commanders to make decisions. There is also a need to review data on decrements in task performance related to changes in pupil size under various conditions of ambient light, including the magnitude and durations of these changes.

- The committee recommends that studies be undertaken to determine whether miosis is the sole cause of operationally relevant performance decrements in humans after low-dose CWA exposure. This research could be done safely in humans with Food and Drug Administration (FDA) approved organophosphate (OP) therapeutic agents and in nonhuman primates with both CWAs and FDA-approved OP agents.
- If cholinesterase levels in the sphincter muscle controlling pupillary constriction do not correlate with functional pupillary changes, then some other mechanism might be responsible for miosis, and a search for alternative macromolecular targets in the ocular tissue might be warranted. The committee recommends that DOD study toxicity end points in addition to cholinesterase inhibition, although tissues (e.g., blood, brain, and eye) should be routinely collected for cholinesterase determinations when animals are killed. Noncholinesterase end points might include fluoride regenerated agent, Na^+/K^+-ATPase, the Comet assay for DNA damage in lymphocytes, toxicogenomics, and cardiac effects (but not a computer model for cardiac arrythmias).
- One of the tasks of the Research Plan is to study neurobehavioral and cognitive changes at CWA doses below those causing overt toxicity in rodents. According to DOD, neurobehavioral tests, such as the functional observational battery, identify changes in central and peripheral nervous system function beyond those observable as clinical signs of intoxication. The committee understands that animal studies focusing on alterations in behavior are difficult to use when extrapolations must be made across species and to humans. The committee concludes that nonhuman primates are better animal models than rodents for subtle behavior changes in humans. The committee recommends that DOD conduct neurobehavior studies in nonhuman primates. In such animal studies and other studies proposed in the Research Plan, good laboratory practice (GLP) standards must be followed, but no evidence of GLP documentation was presented to the committee. The committee also recommends that DOD identify a behavior, if one exists, that is associated with miosis

and that occurs after systemic (inhalation) or topical (ophthalmic) exposure to CWAs. Review of existing data collected from experiments in humans or nonhuman primates would be of value. Regardless of the particular behavior tests to be used, the committee recommends that consideration be given to evaluating adaptive changes in behavior after repeated low-level exposure to CWAs.

- The committee assigns a high priority to those research tasks that study performance degradation. Performance decrements in humans could be caused by miosis or by more subtle neurophysiologic changes unrelated to miosis. Conducting accurate range-finding studies in a nonhuman primate model will be more useful than extrapolating a maximum tolerated dose from a rodent model or using a dose of CWA that shows an effect in rodents, the method recommended in the Research Plan.

- The committee recommends that data from previous studies on the effects of CWAs on military personnel be reevaluated as potentially useful sources with respect to end points of importance in humans. Between 1958 and 1975, the U.S. Army undertook a human volunteer study of 4,826 subjects to investigate the immediate and long-term effects of various classes of chemicals with warfare potential. The results of that study were perviously reviewed by the National Research Council (NRC) Committee on Toxicology. The committee's first report (NRC 1982) found no evidence to support a finding of adverse long-term or delayed health effects after exposure to nerve agents. However, that report was unable to rule out the possibility that some nerve agents produced long-term adverse health effects in some individuals. In the follow-up NRC study (NRC 1985), 4,000 subjects were sent a health questionnaire. The results indicated that subjects who received nerve agents as a group did not differ from controls who did not receive that chemical treatment, but mortality was lower than expected in the exposed population. DOD also should review the database used to derive acute exposure guideline levels (AEGLs) for nerve agents and sulfur mustard recently published by NRC (2003).

- One of the major tasks of the Research Plan is to develop a method to generate consistent vapor atmospheres for GB across a range of relevant concentrations and exposure durations and relate fairly robust historical vapor generation data to modern, validated chamber exposure methodology. The committee is aware that conducting experiments with potent, volatile CWAs having very steep dose-response curves is exceedingly difficult. The committee concludes that DOD's proposed research to overcome technical challenges to generate consistent vapor atmos-

pheres for CWAs and the deployment of sampling and analytical systems is appropriate, and the committee recommends that such research be continued.

- The military commander or decision maker must have the ability to know if a CWA is present in the ambient air, at what concentration, and whether this concentration can induce adverse operational impairments (performance decrements) or adverse delayed health effects in exposed personnel. However, there are limitations in the detection and measurement of CWAs. The committee recommends that DOD strive to develop more sensitive monitors capable of detecting concentrations of CWAs that can cause performance decrements or potential delayed health effects in an operational setting. The committee also recommends that the degree of detection sensitivity required should be driven by an understanding of CWA toxicology—that is, field-operation detector sensitivity that can identify CWA concentrations that are expected to result in operationally relevant performance decrements or immediate health effects.

- The methodology developed for deriving AEGLs is very pertinent. The generalization of Haber's law to adverse effects related to $C^n t$ (ten Berge method) is a valuable contribution. The committee recommends that DOD utilize information and techniques developed for deriving AEGLs.

- In a deployed military setting, being too protective can be as lethal as being insufficiently protected. Protective equipment not only interferes with an individual's ability to fight, it can also cause significant heat stress. Full protective gear—donning mission-oriented protective posture, level 4 (MOPP4)—can restrict movement and vision and causes dehydration and hyperthermia when used in hot climates. It is critical that operational doctrine not require maximal physically protective measures at exposure concentrations significantly below those likely to produce casualties or long-term disabilities. Therefore, the committee recommends that science-based exposure standards (human toxicity estimates) be determined as accurately as possible and that appropriate toxicologic data be developed to minimize the uncertainty around those values.

- One goal of the Research Plan is to develop biomarkers of CWA exposure and to develop consistent measures directly related to the absorbed dose and physiologic effectiveness of a given chemical agent. The goal is also to demonstrate that the dose-metric profile for exposures in animal models enables direct extrapolation to human physiology.

Proposed biomarkers and dose metrics include alkyl phosphonates, regenerated nerve agent, acetylcholinesterase activity, and butyrylcholinesterase activity. The committee concludes that the proposed research on biomarkers is appropriate and recommends that such studies focus on effects from low-level exposure, paying particular attention to fluoride regeneration of the agent.

- One of the tasks of the Research Plan is to characterize the concentration-time relationship (dose-response) for low-level and longer-time CWA exposures (primarily for miosis and mortality end points). The committee recommends that relevant routes of exposure (e.g., inhalation and local exposure of the eye) be specifically evaluated. The setting of exposure limits for CWAs usually involves extrapolation to concentrations or durations of interest by invoking Haber's law—adverse response is related to the product of agent concentration and exposure duration—or the approach of ten Berge (ten Berge et al. 1986), a generalization of Haber's law stating that adverse response is related to $C^n t$. That expression weighs (1) concentration more than time (when $n > 1$), (2) concentration less than time (when $n < 1$), and (3) concentration and time equally (when $n = 1$). The committee recommends that Haber's law not be applied in the absence of data, because naive applications of Haber's law can lead to erroneous risk estimates. Physiologically based pharmacokinetic modeling can be used to improve the evaluation of concentration-duration-response relationships. Mechanistic considerations also would be informative regarding the conditions and dose metrics for which Haber's law is and is not applicable. In the absence of such mechanistic information, the committee recommends that studies be conducted to test and validate duration-exposure models.
- The committee recommends that the DOD develop and apply appropriate statistical models that include concentration of the agent and duration of exposure as predictor variables along with important covariates that allow for testing various extrapolation methods (e.g., Haber's law and ten Berge's law). To ensure that studies include sufficient sample size, statistical principles of design should be used. Exposure concentrations, durations, and routes of exposure should be selected to include realistic scenarios. To facilitate evaluation of the concentration-time relationship, the committee recommends that exposure-response studies be conducted with a minimum of nine concentration-time treatments (three exposure concentrations crossed with three exposure durations).

- To carry out the operational risk management concept, the risk assessor will require robust information on response probabilities from the experimental study. For CWAs, for each critical response (e.g., miosis), the committee recommends that access to recently generated experimental data sets and contact with investigators be sought to develop response probabilities needed in operational risk assessment beyond single values, such as ECt_{50} (the concentration and time that causes an effect in 50% of subjects).
- Field commanders ultimately must be able to use the information generated by this Research Plan to make decisions. The committee recommends that the DOD risk assessors confer with operations personnel to determine the nature and form of information that would be most useful to field commanders. The committee also recommends consultation with risk communication specialists to further assist with this task.
- One of the tasks of the Research Plan is to identify polymorphisms in human blood esterases and other enzymes or genes to identify susceptible subpopulations. Some proportion of the U.S. population might have genetically determined low levels of plasma cholinesterase and thus unusual susceptibility to some anticholinesterase compounds. Several studies indicate that plasma and red-blood-cell cholinesterase activity is significantly lower in women than in men. Therefore, women might be at a greater risk from systemic exposure to OP compounds. Other enzymes, such as paraoxonase and carboxylesterase, involved in nerve agent toxicity also show polymorphisms, which might result in greater susceptibility in personnel with particular genotypes. This research might be helpful in protecting such individuals using proper risk management strategies.

OVERALL EVALUATION OF THE RESEARCH PLAN

The committee recognizes that a considerable amount of research has been done, and much information is available on the acute and subchronic toxicities (delayed effects) of nerve agents and sulfur mustard. Genetic testing, neurotoxicity testing, metabolic studies, and other research studies have been done. The committee recommends that such studies not be repeated. The committee recommends that the Research Plan not attempt to fill in all the data gaps—that is, investigation in numerous species using multiple dosages by various routes of administra-

tion. The time, money, and effort could be better used in focusing on the most important and promising animal models and toxicity end points. The operational relevance of the research in terms of relevant durations of exposure and CWA concentrations must be considered in establishing research priorities.

To obtain the information most valuable in protecting military personnel from operationally significant performance decrements or potential delayed adverse health effects after short-term exposure to low concnetrations of CWAs, DOD should ensure that the total database from previous human and animal studies has been fully examined to fill data gaps. These studies include human studies, nonhuman primate studies, toxicokinetic studies, and the studies used to derive NRC's AEGLs.

Review of the Department of Defense Research Program on Low-Level Exposures to Chemical Warfare Agents

Committee on Toxicologic Assessment of Low-Level Exposures to Chemical Warfare Agents

Committee on Toxicology

Board on Environmental Studies and Toxicology

Division on Earth and Life Studies

NATIONAL RESEARCH COUNCIL
OF THE NATIONAL ACADEMIES

THE NATIONAL ACADEMIES PRESS
Washington, D.C.
www.nap.edu

THE NATIONAL ACADEMIES PRESS 500 Fifth Street, NW Washington, DC 20001

NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

This project was supported by Contract No. W81K04-05-C-7006 and DAMD17-99-C-9049 between the National Academy of Sciences and the U.S. Army. Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the author(s) and do not necessarily reflect the view of the organizations or agencies that provided support for this project.

International Standard Book Number 0-309-10021-6

Additional copies of this report are available from:

The National Academies Press
500 Fifth Street, NW
Box 285
Washington, DC 20055

800-624-6242
202-334-3313 (in the Washington metropolitan area)
http://www.nap.edu

Printed in the United States of America

THE NATIONAL ACADEMIES

Advisers to the Nation on Science, Engineering, and Medicine

The **National Academy of Sciences** is a private, nonprofit, self-perpetuating society of distinguished scholars engaged in scientific and engineering research, dedicated to the furtherance of science and technology and to their use for the general welfare. Upon the authority of the charter granted to it by the Congress in 1863, the Academy has a mandate that requires it to advise the federal government on scientific and technical matters. Dr. Ralph J. Cicerone is president of the National Academy of Sciences.

The **National Academy of Engineering** was established in 1964, under the charter of the National Academy of Sciences, as a parallel organization of outstanding engineers. It is autonomous in its administration and in the selection of its members, sharing with the National Academy of Sciences the responsibility for advising the federal government. The National Academy of Engineering also sponsors engineering programs aimed at meeting national needs, encourages education and research, and recognizes the superior achievements of engineers. Dr. Wm. A. Wulf is president of the National Academy of Engineering.

The **Institute of Medicine** was established in 1970 by the National Academy of Sciences to secure the services of eminent members of appropriate professions in the examination of policy matters pertaining to the health of the public. The Institute acts under the responsibility given to the National Academy of Sciences by its congressional charter to be an adviser to the federal government and, upon its own initiative, to identify issues of medical care, research, and education. Dr. Harvey V. Fineberg is president of the Institute of Medicine.

The **National Research Council** was organized by the National Academy of Sciences in 1916 to associate the broad community of science and technology with the Academy's purposes of furthering knowledge and advising the federal government. Functioning in accordance with general policies determined by the Academy, the Council has become the principal operating agency of both the National Academy of Sciences and the National Academy of Engineering in providing services to the government, the public, and the scientific and engineering communities. The Council is administered jointly by both Academies and the Institute of Medicine. Dr. Ralph J. Cicerone and Dr. Wm. A. Wulf are chair and vice chair, respectively, of the National Research Council.

www.national-academies.org

COMMITTEE ON TOXICOLOGIC ASSESSMENT OF LOW-LEVEL EXPOSURES TO CHEMICAL WARFARE AGENTS

Members

GARY P. CARLSON *(Chair),* Purdue University, West Lafayette, IN
A. JOHN BAILER, Miami University, Oxford, OH
JONATHAN BORAK, Yale School of Medicine, New Haven, CT
JANICE E. CHAMBERS, Mississippi State University, Mississippi State
MARION EHRICH, Virginia Tech, Blacksburg
LYNNE HABER, Toxicology Excellence for Risk Assessment, Cincinnati, OH
SANFORD S. LEFFINGWELL, HLM Consultants, Auburn, GA
DAVID H. MOORE, Battelle Eastern Science and Technology Center, Aberdeen, MD
CAREY POPE, Oklahoma State University, Stillwater
PETER S. SPENCER, Oregon Health & Science University, Portland
NGA LIEN TRAN, Exponent, Inc., Washington, DC

NRC Staff

KULBIR S. BAKSHI, Project Director
CAY BUTLER, Editor
AIDA C. NEEL, Program Associate
ALEXANDRA STUPPLE, Senior Editorial Assistant

COMMITTEE ON TOXICOLOGY

Members

BAILUS WALKER, JR. *(Chair*), Howard University Medical Center and American Public Health Association, Washington, DC
MELVIN E. ANDERSEN, CIIT-Centers for Health Research, Research Triangle Park**,** NC
EDWARD C. BISHOP, Parsons Corporation, Fairfax, VA
GARY P. CARLSON, Purdue University, West Lafayette, IN
JANICE E. CHAMBERS, Mississippi State University, Mississippi State
LEONARD CHIAZZE, JR., Georgetown University, Washington, DC
JUDITH A. GRAHAM, American Chemistry Council, Arlington, VA
SIDNEY GREEN, Howard University, Washington, DC
MERYL KAROL, University of Pittsburgh, Pittsburgh, PA
STEPHEN U. LESTER, Center for Health Environment and Justice, Falls Church, VA
DAVID H. MOORE, Battelle Memorial Institute, Bel Air, MD
CALVIN C. WILLHITE, State of California, Berkeley, CA
GERALD WOGAN, Massachusetts Institute of Technology, Cambridge

Staff

KULBIR S. BAKSHI, Project Director
SUSAN N.J. MARTEL, Senior Program Officer
ELLEN K. MANTUS, Senior Program Officer
AIDA NEEL, Program Associate
TAMARA DAWSON, Senior Program Assistant
ALEXANDRA STUPPLE, Senior Editorial Assistant
SAM BARDLEY, Librarian

[1]This study was planned, overseen, and supported by the Board on Environmental Studies and Toxicology.

OTHER REPORTS OF THE BOARD ON ENVIRONMENTAL STUDIES AND TOXICOLOGY

Health Implications of Perchlorate Ingestion (2005)
Air Quality Management in the United States (2004)
Endangered and Threatened Species of the Platte River (2004)
Atlantic Salmon in Maine (2004)
Endangered and Threatened Fishes in the Klamath River Basin (2004)
Cumulative Environmental Effects of Alaska North Slope Oil and Gas Development (2003)
Estimating the Public Health Benefits of Proposed Air Pollution Regulations (2002)
Biosolids Applied to Land: Advancing Standards and Practices (2002)
The Airliner Cabin Environment and Health of Passengers and Crew (2002)
Arsenic in Drinking Water: 2001 Update (2001)
Evaluating Vehicle Emissions Inspection and Maintenance Programs (2001)
Compensating for Wetland Losses Under the Clean Water Act (2001)
A Risk-Management Strategy for PCB-Contaminated Sediments (2001)
Acute Exposure Guideline Levels for Selected Airborne Chemicals (4 volumes, 2000-2004)
Toxicological Effects of Methylmercury (2000)
Strengthening Science at the U.S. Environmental Protection Agency (2000)
Scientific Frontiers in Developmental Toxicology and Risk Assessment (2000)
Ecological Indicators for the Nation (2000)
Waste Incineration and Public Health (1999)
Hormonally Active Agents in the Environment (1999)
Research Priorities for Airborne Particulate Matter (4 volumes, 1998-2004)
The National Research Council's Committee on Toxicology: The First 50 Years (1997)
Carcinogens and Anticarcinogens in the Human Diet (1996)
Upstream: Salmon and Society in the Pacific Northwest (1996)
Science and the Endangered Species Act (1995)
Wetlands: Characteristics and Boundaries (1995)
Biologic Markers (5 volumes, 1989-1995)
Review of EPA's Environmental Monitoring and Assessment Program (3 volumes, 1994-1995)
Science and Judgment in Risk Assessment (1994)
Pesticides in the Diets of Infants and Children (1993)
Dolphins and the Tuna Industry (1992)
Science and the National Parks (1992)
Human Exposure Assessment for Airborne Pollutants (1991)
Rethinking the Ozone Problem in Urban and Regional Air Pollution (1991)
Decline of the Sea Turtles (1990)

Copies of these reports may be ordered from the National Academies Press
(800) 624-6242 or (202) 334-3313
www.nap.edu

OTHER REPORTS OF THE COMMITTEE ON TOXICOLOGY

Spacecraft Water Exposure Guidelines for Selected Contaminants, Volume 1 (2004)
Toxicologic Assessment of Jet-Propulsion Fuel 8 (2003)
Review of Submarine Escape Action Levels for Selected Chemicals (2002)
Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals (2001)
Evaluating Chemical and Other Agent Exposures for Reproductive and Developmental Toxicity (2001)
Acute Exposure Guideline Levels for Selected Airborne Contaminants, Volume 1 (2000), Volume 2 (2002), Volume 3 (2003), Volume 4 (2004)
Review of the US Navy's Human Health Risk Assessment of the Naval Air Facility at Atsugi, Japan (2000)
Methods for Developing Spacecraft Water Exposure Guidelines (2000)
Review of the U.S. Navy Environmental Health Center's Health-Hazard Assessment Process (2000)
Review of the U.S. Navy's Exposure Standard for Manufactured Vitreous Fibers (2000)
Re-Evaluation of Drinking-Water Guidelines for Diisopropyl Methylphosphonate (2000)
Submarine Exposure Guidance Levels for Selected Hydrofluorocarbons: HFC-236fa, HFC-23, and HFC-404a (2000)
Review of the U.S. Army's Health Risk Assessments for Oral Exposure to Six Chemical-Warfare Agents (1999)
Toxicity of Military Smokes and Obscurants, Volume 1(1997), Volume 2 (1999), Volume 3 (1999)
Assessment of Exposure-Response Functions for Rocket-Emission Toxicants (1998)
Toxicity of Alternatives to Chlorofluorocarbons: HFC-134a and HCFC-123 (1996)
Permissible Exposure Levels for Selected Military Fuel Vapors (1996)
Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants, Volume 1 (1994), Volume 2 (1996), Volume 3 (1996), Volume 4 (2000)

Preface

In 1998, Congress directed the Secretary of Defense to review and modify U.S. Department of Defense (DOD) policies and doctrines that relate to protecting personnel from low-level exposure to chemical warfare agents (CWAs). In response to that congressional mandate, the Secretary of Defense directed DOD's Nuclear, Chemical, and Biological Defense Program to develop a research plan to obtain toxicologic and other data to assess health risks to U.S. forces. The data obtained from the proposed research would provide information to the Secretary of Defense to reassess policies and doctrines related to low-level exposures to CWAs. The research is intended to accomplish two objectives. The first is to support operational commanders in the field with information for real-time decision making required to accomplish their missions while not unduly jeopardizing the health and performance capability of their forces. The second is to understand, prevent, or reduce operationally relevant performance decrements, as well as the potential health consequences of low-level exposures that might not manifest immediately but could become evident months or years after exposure.

In response, DOD developed the multiyear research program on low-level exposures to chemical warfare agents entitled *Department of Defense Low-Level Chemical Warfare Agents (CWAs) Exposure Research Master Plan*. DOD requested that the National Research Council (NRC) review that research plan and comment on its adequacy and appropriateness, provide guidance on appropriate risk assessment methods for assessing toxicologic risk from low-level exposures to CWAs, and identify gaps and make recommendations for further research. The NRC

convened the Committee on Toxicologic Assessment of Low-Level Exposures to Chemical Warfare Agents. The committee's report is intended to be helpful in focusing research efforts to improve operational management.

The DOD Low-Level CWA Exposure Research Master Plan (Research Plan) details the military's priorities for research needs and methods to address the effects of low-level agent exposure on operationally relevant performance in military personnel at the time of exposure and on potential delayed adverse health effects at some point after exposure. As stated in the Research Plan, both of these aspects of low-dose exposure "represent different points along the dose-response continuum—not separate problems."

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We thank the following individuals for their review of this report: Barbara Callahan (University Research Engineers and Associates), Donald J. Ecobichon (consultant), Jeffrey W. Fisher (University of Georgia), David Gaylor (Gaylor & Associates), Ramesh C. Gupta (Murray State University), Rogene Henderson (Lovelace Respiratory Research Institute), Robert MacPhail (U.S. Environmental Protection Agency), and George M. Rusch (Honeywell International).

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of the report before its release. The review of this report was overseen by Edward C. Bishop of Parsons Corporation. Appointed by the NRC, he was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

The committee gratefully acknowledges the valuable presentations made by Stephen Channel, Keith R.Vesely, Douglas Somerville, Jeffrey

Gearhart, Sandra Thomson, and Robert Sheridan, all from the Department of Defense. Aida Neel was the program associate, and Cay Butler was the editor. We are grateful to James J. Reisa, director of the Board on Environmental Studies and Toxicology, for his helpful guidance. The committee particularly acknowledges Kulbir Bakshi, project director for the committee, for bringing the report to completion. Finally, we thank all members of the committee for their expertise and dedicated efforts throughout the development of this report.

Gary P. Carlson, *Chair*
Committee on Toxicologic Assessment of Low
Level Exposures to Chemical Warfare Agents

Bailus Walker, *Chair*
Committee on Toxicology

Contents

SUMMARY **1**

1 INTRODUCTION **11**
Background, 13
Charge to the Committee, 14
Organization of Report, 14

2 UNDERSTANDING THE PROBLEM OF LOW-LEVEL EXPOSURE TO CHEMICAL WARFARE AGENTS **16**
Background, 18
Toxicologic Studies, 19
Other Animal Studies, 20
Human Exposures, 20
Chemical Warfare Exposure Scenario, 25
Risk Comparisons, 27

3 REVIEW OF THE DEPARTMENT OF DEFENSE MASTER RESEARCH PLAN ON LOW-LEVEL EXPOSURE TO CHEMICAL WARFARE AGENTS **30**
Goals, Objectives, and Aims of the Master Research Plan, 30
Overview of the DOD's Current Research Plan, 31
The Committee's Evaluation of the DOD Research Plan, 32
Overall Summary of the Evaluation of the DOD Research Plan, 62

4 RESEARCH ISSUES RELATED TO RISK ASSESSMENT OF LOW-LEVEL EXPOSURE TO CHEMICAL WARFARE AGENTS 65
Question 1. What Is the Critical Adverse Response to Exposure to Low Levels of CWAs? 65
Question 2. How Much of a Decrement in the Critical Response is Advserse? 66
Question 3. Are There Biomarkers of CWA Exposure That Can Be Measured and Used in Risk Comparisons? 67
Question 4. How Should Exposures in "Work" Conditions Be Considered When Extrapolating Animal Models to Human Experience? 69
Question 5. What is the Relationship Between Exposure Concentration-Duration and Risk? 70
Question 6. How Should Exposure-Duration Risk Be Communicated for CWAs? 73
Question 7. What Are Appropriate Approaches for Evaluating the Risk of Exposure to a CWA Mixture? 74
Question 8. What Information Is Needed to Best Support Extrapolation from Animal Studies to Human Responses? How and When Might a PBPK Model Be Useful for Aiding in Such Extrapolations? 75
Question 9. What Is the Impact of Experimental Designs on Risk Assessments and Subsequent Efforts to Establish Exposure Guidelines for Military Personnel Protection? 78
Question 10. How Does One Account for Variability in Human Response to CWAs, and Do CWA-Susceptible Subpopulations of Humans Exist? 79
Question 11. What Statistical Models Are Appropriate for Concentration-Time Data? 80
Regression Methods for Continuous or Ordered Responses, 85
Experimental Recommendations, 86
The Committee's Recommendations, 86

REFERENCES 89

ABBREVIATIONS 103

Review of the Department of Defense Research Program on Low-Level Exposures to Chemical Warfare Agents